

3,3'-DIMETHYLBENZIDINE AND DYES METABOLIZED TO 3,3'- DIMETHYLBENZIDINE

INTRODUCTION

3,3'-Dimethylbenzidine was first listed in the *Third Annual Report on Carcinogens* (RoC) in 1983. 3,3'-Dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine (3,3'-Dimethylbenzidine Dyes Class) were first listed in the Tenth Edition of the RoC in 2002.

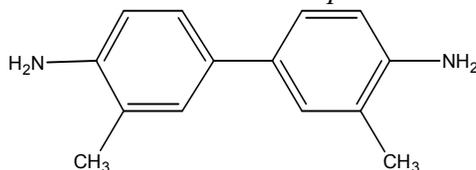
The profiles for 3,3'-dimethylbenzidine and dyes metabolized to 3,3'-dimethylbenzidine follow this introduction. The listings for 3,3'-dimethylbenzidine and dyes metabolized to 3,3'-dimethylbenzidine in the RoC are as follows:

- 3,3'-Dimethylbenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in rats (IARC 1972, NTP 1991,).
- 3,3'-Dimethylbenzidine dyes that are metabolized to 3,3'-dimethylbenzidine are *reasonably anticipated to be human carcinogens* based on the fact that 3,3'-dimethylbenzidine is *reasonably anticipated to be a human carcinogen* (NTP 2000) and the fact that these compounds have the same type of chemical bond (azo linkages), which are easily broken by chemical or enzymatic reduction to form free 3,3'-dimethylbenzidine and the respective chromophore(s). The metabolism of 3,3'-dimethoxybenzidine-based dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied (Lynn *et al.* 1980, Bowman *et al.* 1982).

3,3'-DIMETHYLBENZIDINE

CAS No. 119-93-7

First listed in the *Third Annual Report on Carcinogens*



CARCINOGENICITY

3,3'-Dimethylbenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in rats (IARC 1972, NTP 1991). When given to rats by subcutaneous injection, commercial 3,3'-dimethylbenzidine induced cancer (carcinoma) of the Zymbal gland and ear (external auditory canal). When given to rats in their drinking water, the dihydrochloride salt of 3,3'-dimethylbenzidine increased the incidence of cancer of the Zymbal gland (adenoma and carcinoma), neoplasms and cancer of the liver (neoplastic nodules and hepatocellular carcinoma), cancer of the large intestine (adenomatous polyps and adenocarcinoma), skin cancer (basal cell adenoma and carcinoma), and cancer of the oral cavity (squamous-cell papilloma and carcinoma) in both males and females. Male rats also had increased incidences of cancer of the preputial gland (carcinoma) and small intestine (adenocarcinoma) and neoplasms of the lung, and female rats also had increased incidences of cancer of the clitoral gland (adenoma and carcinoma) and mammary gland (adenocarcinoma).

No adequate human studies of the relationship between exposure to 3,3'-dimethylbenzidine and human cancer have been reported (IARC 1972, 1987).

PROPERTIES

3,3'-Dimethylbenzidine occurs as a white to reddish crystalline powder that is slightly soluble in water and very soluble in ethanol, ethyl ether, and dilute acids. It is produced as technical-grade dry and paste formulations of various purities. When heated to decomposition, it emits toxic fumes of nitrogen oxides (HSDB 2000).

USE

More than 75% of 3,3'-dimethylbenzidine produced is used as a dye or an intermediate for producing dyestuffs and pigments. According to the Society of Dyers and Colourists, more than 95 dyes are derived from 3,3'-dimethylbenzidine. Approximately 20% of 3,3'-dimethylbenzidine is used to produce polyurethane-based high-strength elastomers, coatings, and rigid plastics. 3,3'-Dimethylbenzidine is used in small quantities by clinical laboratories in test tapes for the detection of blood and by water companies, swimming pool owners, and others to test for chlorine in water or air (IARC 1972). 3,3'-Dimethylbenzidine is also used in a chemical test for the detection of gold (HSDB 2000).

PRODUCTION

The 1997 Directory of Chemical Producers identified one producer of 3,3'-dimethylbenzidine, with no production volume reported (SRI 1997). Three U.S. producers of 3,3'-dimethylbenzidine were identified in 1986 and 1985, but no production volumes were reported (SRI 1986, USITC 1987). In 1978, the major company producing 3,3'-dimethylbenzidine in the United States ceased production; its annual production had averaged approximately 200,000 lb (HSDB 2000). Imports appear to be the major source of 3,3'-dimethylbenzidine in the United States. The 1979 Toxic Substances Control Act Inventory identified four companies importing 115,500 lb in 1977. The confidential business information aggregate was between 1 million and 100 million pounds (TSCA 1979). The U.S. International Trade Commission reported imports of 75,000 lb of 3,3'-dimethylbenzidine, and 163,700 lb of its hydrochloride salt in 1983, compared with more than 5,000 lb of 3,3'-dimethylbenzidine hydrochloride in 1980. In 1979, approximately 3.5 million pounds of 3,3'-dimethylbenzidine and 240,000 pounds of the hydrochloride were imported into the United States (USITC 1984). 3,3'-Dimethylbenzidine was imported through the principal U.S. customs districts in 1989, but the quantity was not published. Chem Sources (2001) identified 19 U.S. suppliers of 3,3'-dimethylbenzidine.

EXPOSURE

The primary routes of potential human exposure to 3,3'-dimethylbenzidine are inhalation, dermal contact, and ingestion. Workers potentially exposed to 3,3'-dimethylbenzidine include dye makers, repackagers of 3,3'-dimethylbenzidine and dimethylbenzidine-based dyes, and personnel in clinical and analytical laboratories. Workers in a variety of occupations may be exposed to small quantities of 3,3'-dimethylbenzidine used for analytical purposes, including water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives. Swimming pool water test kits contain 0.5% to 1.0% 3,3'-dimethylbenzidine. Exposure may occur if the test solutions are emptied into the pool. In 1978, the National Institute of Occupational Safety and Health (NIOSH) estimated that fewer than 100 employees were exposed to large quantities of 3,3'-dimethylbenzidine in the United States, but as many as 200,000 may have been exposed to small quantities (NIOSH 1979). The National Occupational Exposure Survey (1981 to 1983) estimated that 8,676 workers, including 5,383 women, potentially were exposed to 3,3'-dimethylbenzidine (NIOSH 1984). This estimate was based on observations of actual use of the compound (62% of total observations) and the use of trade-name products known to contain the compound (38%). The National Occupational Exposure Survey conducted by NIOSH between 1981 and 1983 estimated that 9,639 workers potentially were exposed to 3,3'-Dimethylbenzidine (NIOSH 1990).

Dimethylbenzidine-based dyes and pigments break down to form 3,3'-dimethylbenzidine. Residual levels of 3,3'-dimethylbenzidine may be present in dimethylbenzidine-based dyes and pigments and in the final consumer products. Available data indicate that such contaminants occur in the parts-per-million range. A dimethylbenzidine-based dye was not absorbed dermally to any substantial degree when tested in rabbits. _

The U.S. Environmental Protection Agency's (EPA's) Toxic Chemical Release Inventory reported that one facility produced, processed, or otherwise used 3,3'-dimethylbenzidine in the United States in 1996. The facility, reporting under the industrial classification for manufacture of cyclic crudes and intermediates (SIC Code 2865), released a total of 6 lb to air and 25 lb to water (TRI96 1998). In 1999, three facilities reportedly produced, processed, or otherwise used

3,3'-dimethylbenzidine in the United States. Total air emissions were 17 lb, and 1 lb was released to surface water (TRI99 2001).

REGULATIONS

In 1980, the U.S. Consumer Product and Safety Commission (CPSC) collected economic and toxicological data in support of a proposed ban on the use of benzidine-based dyes in direct consumer dye products. CPSC also conducted studies on the dermal penetration of two benzidine congener dyes with negative results. The use of benzidine congener dyes in consumer products and commercial textile applications has been decreased voluntarily. Therefore, CPSC did not ban these consumer dye products. Consumer products containing benzidine congener dyes that are packaged or marketed as art and craft materials may be subject to specific procedural and labeling requirements under the Labeling of Hazardous Art Materials Act.

EPA regulates 3,3'-dimethylbenzidine under the Resource Conservation and Recovery Act as a hazardous constituent of waste and has established a reportable quantity of 10 lb under the Comprehensive Environmental Response, Compensation, and Liability Act. Under the Superfund Amendments and Reauthorization Act, 3,3'-dimethylbenzidine was placed on a list of toxic chemicals subject to reporting requirements, and general threshold quantities have been established for facilities using or producing the compound.

NIOSH recommends a 20- $\mu\text{g}/\text{m}^3$ ceiling for 3,3'-dimethylbenzidine exposure in the workplace, with no skin contact. The Occupational Safety and Health Administration regulates this compound under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 75.

REFERENCES

Chem Sources. Chemical Sources International, Inc., <http://www.chemsources.com>, 2001.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. 3,3'-dimethylbenzidine. Profile last updated May 21, 2000. Last review date, November 1, 1994.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds and Natural Products. Vol. 1. Lyon, France: IARC, 1972, 184 pp.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity. Supplement 7. Lyon, France: IARC, 1987, 440 pp.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Hazard Survey (1972-74). Cincinnati, OH: Department of Health, Education, and Welfare, 1976.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (NOES) (1981-1983). Unpublished provisional data as of July 1, 1990, Cincinnati OH

NIOSH. National Institute for Occupational Safety and Health. A Recommended Standard for Occupational Exposure to *o*-Tolidine. Cincinnati, OH: Department of Health, Education, and Welfare, 1979, 9 pp.

NTP. National Toxicology Program. Toxicology and Carcinogenesis Studies of 3,3'-Dimethylbenzidine Dihydrochloride in F344/N Rats (Drinking Water Studies). (TR-390), 231 pp. National Toxicology Program Technical Report Series, 1991.

SRI. Directory of Chemical Producers, United States, 1985. Stanford Research Institute, Menlo Park, CA: SRI International, 1986.

SRI. Directory of Chemical Producers, United States, 1997. Stanford Research Institute, Menlo Park, CA: SRI International, 1997.

TRI96. Toxic Chemicals Release Inventory 1996. Data contained in the Toxic Chemical Release Inventory (TRI). Available from U.S. Environmental Protection Agency, Office of Environmental information. <http://www.epa.gov/triexplorerer/reports.htm>, 1998.

TRI99. Toxic Chemicals Release Inventory 1999. Data contained in the Toxic Chemical Release Inventory (TRI). Available from the U.S. Environmental Protection Agency, Office of Environmental information. <http://www.epa.gov/triexplorerer/reports.htm>, 2001.

TSCA. Toxic Substances Control Act, Chemical Substance Inventory, 1979: public record.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1986. USITC Publication No. 2009. Washington, DC: U.S. Government Printing Office, 1987.

USITC. U.S. International Trade Commission. Imports of Benzenoid Chemicals and Products, 1983. USITC Publication No. 1548. Washington, DC: U.S. Government Printing Office, 1984.

**DYES METABOLIZED TO 3,3'-DIMETHYLBENZIDINE
(3,3'-DIMETHYLBENZIDINE DYE CLASS)**
First listed in the *Tenth Report on Carcinogens*

CARCINOGENICITY

3,3'-Dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine are *reasonably anticipated to be human carcinogens* based on the fact that 3,3'-dimethylbenzidine is carcinogenic in male and female rats (IARC 1972, NTP 1991b, 2000) and the fact that metabolism of 3,3'-dimethylbenzidine-based dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied (Lynn *et al.* 1980, Bowman *et al.* 1982). Furthermore, a representative 3,3'-dimethylbenzidine-based dye, C.I. Acid Red 114, is carcinogenic in male and female rats (NTP 1991a). The pattern of tumors observed with C.I. Acid Red 114 (NTP 1991a) and 3,3'-dimethylbenzidine (NTP 1991b) is similar to that observed with the structurally similar chemical 3,3'-dimethoxybenzidine (NTP 1992) and the 3,3'-dimethoxybenzidine-based dye C.I. Direct Blue 15 (NTP 1992). These four chemicals each induce tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland of male rats, and clitoral gland of female rats, and other tissue sites.

No adequate human studies of the relationship between exposure to 3,3'-dimethylbenzidine-based dyes and human cancer have been reported.

OTHER INFORMATION RELATING TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

3,3'-Dimethylbenzidine is structurally similar to benzidine, a *known human carcinogen* (IARC 1972, 1979, 1982, 1987, NTP 2000), and 3,3'-dimethoxybenzidine, which is *reasonably anticipated to be a human carcinogen* (IARC 1974, NTP 2000). Like benzidine and 3,3'-dimethoxybenzidine, 3,3'-dimethylbenzidine is used to synthesize many dyes, by linking of various chromophores to the base chemical by azo linkages. The azo bonds of 3,3'-dimethylbenzidine-based dyes are chemically similar regardless of the chromophore used, and they are easily broken by chemicals or enzymes via reduction to form free 3,3'-dimethylbenzidine and free chromophore(s). A number of bacteria catalyze this process, including *Escherichia coli*, found in the human gastrointestinal tract (Cerniglia *et al.* 1982, Morgan *et al.* 1994). This reductive process also has been found in rats, dogs, and hamsters (Lynn *et al.* 1980, Bowman *et al.* 1983, Nony *et al.* 1983). Bacteria in the animals' gastrointestinal tract are thought to be the primary agents of this metabolism in animals (Cerniglia *et al.* 1982, Morgan *et al.* 1994). 3,3'-Dimethylbenzidine-based dyes are mutagenic in bacteria when tested with metabolic activation and an azo-reductive preincubation protocol (NTP 1991a). It is assumed that the breakdown process results in the formation of 3,3'-dimethylbenzidine, known to cause mutations in bacteria (Haworth *et al.* 1983).

No available information suggests that mechanisms by which these substances cause cancer in laboratory animals would not also operate in humans.

PROPERTIES

3,3'-Dimethylbenzidine occurs as white to reddish crystals or crystalline powder. It is used in dye production and is sensitive to light and prolonged exposure to air (NTP 2001). 3,3'-Dimethylbenzidine is a strong oxidizer (NIOSH 1994); it is slightly soluble in water and 95% ethanol and soluble in dimethylsulfoxide, acetone, alcohol, ether, and dilute acids. When heated to decomposition, it emits toxic fumes of nitrogen oxides (Sax 1984).

USE

According to the Society of Dyers and Colourists, more than 95 dyes are derived from 3,3'-dimethylbenzidine. More than 75% of 3,3'-dimethylbenzidine produced is used as a dye or an intermediate for producing of 3,3'-dimethylbenzidine-based dyes. These dyes and pigments are used in printing textiles, as biological stains, and in color photography. Approximately 20% of 3,3'-dimethylbenzidine is used to produce polyurethane-based high-strength elastomers, coatings, and rigid plastics. 3,3'-Dimethylbenzidine also is used in chemical tests for detecting gold and chlorine in water and as a curing agent for resins (Budavari 1996, Spectrum 1999, HSDB 2001).

PRODUCTION

The U.S. International Trade Commission (USITC 1994) reported that 3,3'-dimethylbenzidine was produced by two companies and 3,3'-dimethylbenzidine-based dyes were produced by three companies. Current production volumes for individual producers are not reported because they are confidential for both importers and producers of 3,3'-dimethylbenzidine. Annual U.S. production and imports of various 3,3'-dimethylbenzidine-based dyes ranged from approximately 7,500 lb to more than 180,000 lb (USITC 1980, 1981, 1984, 1994).

EXPOSURE

Most environmental exposures to 3,3'-dimethylbenzidine occur through contact with industrially contaminated air, water, or soil (HSDB 2001). The general population may be exposed via contact with paper, fabric, or leather products containing 3,3'-dimethylbenzidine-based dyes.

Most occupational exposures to 3,3'-dimethylbenzidine and 3,3'-dimethylbenzidine-based dyes are of workers in dye manufacturing and processing plants. Occupational exposure may occur by inhalation of dust or mist, accidental ingestion, or dermal contact. In 1986 and 1987, EPA, the American Textile Manufacturers Institute, and the Toxicological Association of the Dyestuffs Manufacturing Industry conducted a joint survey to estimate airborne concentrations of dye dust in dye-weighing rooms of facilities where powdered dyes were used to dye and print textiles. The estimated mean airborne concentration of total dye in 24 randomly monitored plants was 0.085 mg/m³ (EPA 1990).

The National Occupational Exposure Survey (NIOSH 1990) estimated that 9,639 workers potentially were exposed to 3,3'-dimethylbenzidine between 1981 to 1983. (NIOSH 1990)

Workers in other occupations may be exposed to small quantities of 3,3'-dimethylbenzidine and 3,3'-dimethylbenzidine-based dyes. These workers include water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives. Swimming pool water test kits contain 0.5% to 1.0% 3,3'-dimethylbenzidine, and exposure may occur if the test solutions are emptied into the pool. Chemists also may be exposed in the laboratory when using 3,3'-dimethylbenzidine to detect free chlorine or gold (NTP 1998).

REGULATIONS

In 1980, the U.S. Consumer Product and Safety Commission collected economic and toxicological data in support of a proposed ban on the use of benzidine-based dyes in direct consumer dye products. The CSPC also conducted studies on the dermal penetration of two benzidine congener dyes, with negative results. The use of benzidine congener dyes in consumer products and commercial textile applications has been decreased voluntarily. Therefore, the CSPC did not ban these consumer dye products. Consumer products containing benzidine congener dyes that are packaged or marketed as art and craft materials may be subject to specific procedural and labeling requirements under the Labeling of Hazardous Art Materials Act.

Under the Superfund Amendments and Reauthorization Act, EPA regulates certain dyes (trypan blue and C.I. acid red 114) that are metabolized to 3,3'-dimethylbenzidine. These dyes were placed on a list of toxic chemicals subject to reporting requirements, and general threshold quantities for reporting of releases have been established for facilities using or producing these compounds.

OSHA regulates dyes metabolized to 3,3'-dimethylbenzidine under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 75.

REFERENCES

Bowman, M.C., W.L. Oller, C.R. Nony, K.L. Rowland, and S.M. Billedeau. Metabolism and distribution of two ¹⁴C-benzidine-congener-based dyes in rats as determined by GC, HPLC, and radioassays. *J. Anal. Toxicol.*, Vol. 6, 1982, pp. 164-174.

Bowman, M.C., C.R. Nony, S.M. Billedeau, J.L. Martin, H.C.J. Thompson, and L.K. Lowry. Metabolism of nine benzidine-congener-based azo dyes in rats based on gas chromatographic assays of the urine for potentially carcinogenic metabolites. *J. Anal. Toxicol.*, Vol. 7, 1983, pp. 55-60.

Budavari, S, M. J. O'Neil, A. Smith, and P.E. Heckelman (eds.). *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*. 12th ed.. Whitehouse Station, NJ: Merck & Co., Inc., 1996, p. 1498.

Cerniglia, C.E., J.P. Freeman, W. Franklin, and L.D. Pack. Metabolism of azo dyes derived from benzidine, 3,3'-dimethyl-benzidine and 3,3'-dimethoxybenzidine to potentially carcinogenic aromatic amines by intestinal bacteria. *Carcinogenesis*, Vol. 3. 1982, pp. 1255-1260.

EPA. U.S. Environmental Protection Agency. Textile Dye Weighing Monitoring Study. EPA Report No. EPA-560/5-90-009 (main report and site visit reports). Washington, DC: U.S. EPA Office of Toxic Substances, 1990.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen., Vol. 5, 1983, pp. 3-142.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. 3,3'-Dimethylbenzidine. Profile last updated May 16, 2001. Last review date, November 7, 1991.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds and Natural Products. Vol. 1. Lyon, France: IARC, 1972, pp. 87-91.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents. Vol. 4. Lyon, France: IARC, 1974, 286 pp.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Monomers, Plastics and Synthetic Elastomers, and Acrolein. Vol. 19. Lyon, France: IARC, 1979, 513 pp.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Industrial Chemicals and Dyestuffs. Vol. 29. Lyon, France: IARC, 1982, 416 pp.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Suppl. 7. Lyon, France: IARC, 1987, 440 pp.

Lynn, R.K., D.W. Donielson, A.M. Ilias, J.M. Kennish, K. Wong, and H.B. Matthews. Metabolism of bisazobiphenyl dyes derived from benzidine, 3,3'-dimethylbenzidine or 3,3'-dimethoxybenzidine to carcinogenic aromatic amines in the dog and rat. Toxicol. Appl. Pharmacol., Vol. 56, 1980, pp. 248-258.

Morgan, D.L., J.K. Dunnick, T. Goehl, M.P. Jokinen, H.B. Matthews, E. Zeiger, and J.H. Mennear. Summary of the National Toxicology Program benzidine dye initiative. Environ. Health Perspect., Vol. 102, 1994, pp. 63-77.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (NOES) (1981-1983). unpublished provisional data as of July 1, 1990. Cincinnati, OH

NIOSH. National Institute for Occupational Safety and Health. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No.94-116. Washington, DC: U.S. Government Printing Office, 1994, p. 311.

Nony, C.R., J.L. Martin, and M.C. Bowman. Metabolism of a dimethylbenzidine-based dye in rats and hamsters as determined by analysis of the urine for potentially carcinogenic aromatic amines. J. Anal. Toxicol., Vol. 7, 1983, pp. 49-54.

NTP. National Toxicology Program. Toxicology and Carcinogenesis Studies of C.I. Acid Red 114 (CAS No. 6459-94-5) in F344/N Rats (Drinking Water Studies). Technical Report Series TR-405. Research Triangle Park, NC: NTP, 1991a.

NTP. National Toxicology Program. Toxicology and Carcinogenesis Studies of 3,3'-Dimethylbenzidine Dihydrochloride in F344/N Rats (Drinking Water Studies). Technical Report Series TR-390. Research Triangle Park, NC: NTP, 1991b, 231 pp.

NTP. National Toxicology Program. Toxicology and Carcinogenesis Studies of C.I. Direct Blue 15 in F344/N rats. Technical Report Series TR-397. Research Triangle Park, NC: NTP, 1992, 249 pp.

NTP. National Toxicology Program. Ninth Report on Carcinogens. 2000. <http://ehp.niehs.nih.gov/roc/toc9.html>.

NTP. National Toxicology Program. NTP Chemical Respository. 3,3'-Dimethylbenzidine. Last updated August 13, 2001. (<http://ntp-server.niehs.nih.gov> & search 119-93-7).

Sax, N.I. Dangerous Properties of Industrial Materials. N.I. Sax and S. R. Lewis, eds. New York: Van Nostrand Reinhold, 1984.

Spectrum. Chemical Fact Sheet for *o*-Tolidine. Spectrum Laboratories, Inc., 1999.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals - United States Production and Sales 1979. USITC Publication No. 1099. Washington, DC: U.S. Government Printing Office, 1980, p. 17.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals - United States Production and Sales 1980. USITC Publication No. 1163. Washington, DC: U.S. Government Printing Office, 1981.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals - United States Production and Sales 1983. USITC Publication No. 1548. Washington, DC: U.S. Government Printing Office, 1984.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals - United States Production and Sales 1993. USITC Publication No. 2933. Washington, DC: U.S. Government Printing Office, 1994.